Oral Presentations

ALLOGENEIC

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THE IMPACT OF METHYLENETETRAHYDROFOLATE REDUCTASE C677T GENE POLYMORPHISM ON ENGRAFTMENT AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS RECEIVING METHOTREXATE IN GRAFT VERSUS HOST DISEASE PROPHYLAXIS

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Methotrexate (MTX) is an antifolate chemotherapeutic drug and is used to prevent graft versus host disease (GVHD) in allogeneic hemapoietic cell transplantation (AHCT). The effectiveness of MTX is largely attributable to its role of MTHR and its gene polymorphism is a common (10-12% homozygote and 40% heterozygote) variation in the population. Depending on to this finding, we investigated whether MTHFR C677T gene polymorphism has any affect on engraftment kinetics of patients undergoing ASCT to whom MTX is given for GVHD prophylaxis. We retrospectively analyzed our cohort of 82 allogeneic stem cell recipients whose MTHFR gene polymorphism of C677T region was analyzed by RT-PCR for the pretransplant evaluation of hereditary thrombophilia. The patient's median age was 31 (range, 14-50) years, with a M/F: 50/32 and diagnosis; 35 AML, 26 CML, 12 ALL and 9 other. Nearly all of the patients were given standard conditioning regimen consisting of BUCY or TBICY. All of the patients received cyclosporine A and short term MTX for GVHD prophylaxis. Stem cell source was bone marrow (BM) in 23 and peripheral blood (PB) in 59 of the patients. MTHFR gene polymorphism was detected in 32 (39%) of all patients, and 90% were heterozygotes (MTHFR HeZ). When we compared the engraftment kinetics, granulocyte engraftment was found to be late in MTHFR HeZ group (neutrophil 1000 median 19 vs 17 days; $P = .01$) but not different for neutrophil 500 and platelet engraftment. We have observed that MTHFR gene polymorphism had a prominent effect on BM recipients, as both neutrophil 500 and 1000 and also platelet engraftments were affected (granulocyte 500 median 21 vs 15 $P = .005$; granulocyte 1000 median 22.5 vs 17 $P = .0001$ and plt 20 median 27 vs 21 $P = .03$) significantly. On the contrary, there was no difference in the PB group. The number of MNC and CD34+ cells were similar in patients with and without gene polymorphism both in BM and PG group. When we compare the side effects of MTX such as nausea and vomiting, diarrhea, mucositis, there was no difference in acute GVHD incidence. Our knowledge on epigenetic data will help us on tailoring the chemotherapy regimen for conditioning and GvHD prophylaxis in transplant recipients. Our data on a limited patient size suggest that the presence of MTHFR HeZ may have an impact on allo HCT recipients engraftment kinetics while using MTX for GVHD prophylaxis and BM as stem cell source.

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SIROLIMUS AND TACROLIMUS WITHOUT METHOTREXATE AS GRAFT-VS.-HOST DISEASE PROPHYLAXIS AFTER MATCHED, UNRELATED PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (PBSCT): EXCELLENT GVHD CONTROL WITH LOW TRANSPLANT-RELATED MORBIDITY AND MORTALITY

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We have previously demonstrated that the combination of sirolimus (rapamycin, Rap), tacrolimus (Tac) and low-dose methotrexate (Mtx) is effective GVHD prophylaxis in URD transplantation, and the combination of Rap and Tac alone is effective in MRD transplantation. Since Mtx is associated with transplant-related toxicity and delayed engraftment, we hypothesized that Rap and Tac, without Mtx, would provide effective GVHD prophylaxis in URD transplantation while minimizing transplant-related morbidity and mortality. **Methods:** 30 subjects underwent PBSCT from 6/6 HLA-matched unrelated donors after Cy/TBI conditioning. GVHD prophylaxis consisted of Rap (target serum level 3-12 ng/ml) and Tac (target serum level 5-10 ng/ml). G-CSF (5 μg/kg) was administered from day +12 until engraftment, if needed. **Results:** The median age of subjects was 44 years (range 22-54). Diagnoses were AML (13), CML (6), NHL (4), MDS (3), ALL (2), MPD (1) and HD (1). The median times to neutrophil (>500/μL) and platelet engraftment (>20000/μL and >100000/μL) were 13.5 (range 11-14), 12 (range 9-25), and 17 (range 12-101) days, respectively. Two patients did not become platelet transfusion independent. All 30 patients survived to first hospital discharge, at a median of 19 days from day 0 (range 14-55). Gr. II-IV acute GVHD occurred in 5 patients (16.7%) with only one case of Gr. IV acute GVHD (3.3%). Transplant-related morbidity was low, without any cases of IPS/DAH. Two subjects developed VOD and one subject developed thrombotic microangiopathy. Reactivation of HHV-6 with limbic encephalitis was noted in 2 patients. 13 of 25 evaluable patients developed chronic GVHD. Five patients relapsed, one of whom achieved a durable complete remission after immunosuppression withdrawal and DLI. Causes of death include relapse (3), VOD (1), and relapse with VOD and hepatic GVHD (1). The median follow-up is 230 days (range 46-608). Treatment-related mortality at 100 days is 3.3%. Relapse-free and overall survival at day 100 are both 93.1%, and at 1 year are 78.1% and 80.9%, respectively. **Conclusions:** Rap and Tac without Mtx is effective for GVHD prophylaxis after matched URD PBSCT, leading to acute GVHD in 16.7% of treated patients, which is similar to our experience using Rap and Tac in MRD transplantation. Furthermore, the omission of Mtx is associated with minimal transplant-related morbidity and mortality at 100 days. This combination is worthy of broader study in unrelated donor transplantation.

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MEASURING MULTIPLE SYMPTOMS AND INFLAMMATORY CYTOKINES RELATED TO ACUTE GVHD IN AML/MDS PATIENTS UNDERGOING ALLOGENEIC BMT

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The objective of this study was to prospectively assess the relationship between symptom severity and changes in inflammatory cytokines around the time of diagnosis of acute GVHD in AML/MDS patients during the first 100 days of allo-BMT. **Methods:** Weekly symptom assessment with the M. D. Anderson Symptom Inventory was done for 30 patients for the first 100 days following BMT. A panel of inflammatory cytokines (IL-1ra, IL-6, IL-8, IL-10, IL-12, TNF-α) was assayed at multiple time points (pre-BMT, conditioning, day of BMT, BMT day +1, nadir, BMT days +8, +14, +21, +28, +60, and +90-100, also days 1, 3, 5, 10 and 15 of diagnosis of acute GVHD for the 26 patients who developed it). **Results:** Of the 26 patients who developed acute GVHD, 69% had grade 1 GVHD, 27% had grade 2, and 4% had grade 3. 42% were treated systemically with a dose of 2 mg/kg of steroids, and 31% were treated with topical steroids alone. Non-specific symptoms experienced by these patients reached their highest levels shortly before the day of diagnosis of acute GVHD. Immediate symptom reduction occurred after diagnosis of acute GVHD and was most likely caused by administration of steroids. IL-8 was significantly correlated with some symptoms before and after diagnosis of acute GVHD (Table 1). **Conclusion:** During development of GVHD in the acute phase of allo-BMT, there was an observed relationship of severity of certain symptoms and increased or decreased inflammatory cytokine levels in this pilot